Diagnosis, Assessment, and Therapeutic Strategy for Colorectal Mixed Adenoneuroendocrine Carcinoma

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Abstract

Colorectal mixed adenoneuroendocrine carcinoma (MANEC), which acts like an aggressive tumor, is a rare clinical manifestation on which only a limited amount of literature exists. Surgical resection by regional lymphadenectomy is considered as the only curative treatment for colorectal MANEC, and adjuvant chemotherapy or radiotherapy is recommended because of its high recurrence rate. Colorectal MANEC is frequently diagnosed at an advanced stage, when it is unresectable, and chemotherapy plays a central role in its treatment. Pathological confirmation of the target lesion component is critical for regimen selection. If the lesion comprises an adenocarcinomatous component, a regimen for colorectal adenocarcinoma should be administered. For lesions comprising mainly a neuroendocrine carcinomatous component, cisplatin combined with etoposide or irinotecan has proven to be clinically appropriate. Everolimus, a mechanistic target of rapamycin pathway inhibitor, also improves survival. Sunitinib malate, another molecular target-

ing agent, is effective for treating neuroendocrine carcinoma; however, the evidence on its effectiveness for treating gastrointestinal neuroendocrine carcinoma is insufficient.

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Introduction

Neuroendocrine tumors account for a minority of cases of gastrointestinal tumors [1]; however, the incidence of these tumors is gradually increasing according to the Surveillance, Epidemiology, and End Results database of the USA [2]. The rectum is the most common primary site of gastrointestinal neuroendocrine tumors, followed by the jejunum/ileum, stomach, and colon. The distribution of these tumors differs by race and sex. According to the World Health Organization in 2010, neuroendocrine tumors are classified as G1, G2, or G3 (neuroendocrine carcinoma) based on the mitotic count or Ki-67 index (Table 1). Mixed adenoneuroendocrine carcinoma (MANEC) comprises neoplasms containing both neuroendocrine carcinomatous and adenocarcinomatous components. To meet the definition of MANEC, both com-

Fig. 1. Colonoscopic (**a, c**) and CT (**b, d**) images of rectal mixed adenoneuroendocrine carcinoma at initial diagnosis (**a, b**) and 4 weeks after neoadjuvant chemoradiotherapy (**c, d**).

Table 1. World Health Organization 2010 classification of NETs

Grade	Gastroenteropancreatic NET	Lung and thymus	Differentiation
Low (G1)	<2 mitoses/10 HPFs and/or Ki-67 index <3%	<2 mitoses/10 HPFs and no necrosis	Well-differentiated NET
Intermediate (G2)	2–20 mitoses/10 HPFs and/or Ki-67 index 3–20%	2–10 mitoses/10 HPFs and/or foci of necrosis	Well-differentiated NET
High (G3)	>20 mitoses/10 HPFs and/or Ki-67 index >20%	>10 mitoses/10 HPFs	Poorly differentiated neuroendocrine carcinoma

NET, neuroendocrine tumor; HPF, high-power field.

ponents must constitute at least 30% of the tumor and be separately graded as carcinomas [3].

Owing to this dual histology, the clinical behavior of MANEC differs from that of neuroendocrine carcinoma or adenocarcinoma; however, no clinical practice guidelines have yet been developed, and the National Comprehensive Cancer Network (NCCN) guidelines (version 1.02017) do not include the management of MANEC. Furthermore, only a limited number of studies on MANEC have been published. Herein, we review these studies and discuss the clinicopathological features, therapeutic options, and outcomes of colorectal MANEC.

Diagnosis of MANEC

Colonoscopic Examination

Colonoscopy is the most reliable modality for the definite diagnosis of colorectal neoplasms. Reportedly, neuroendocrine carcinoma progresses rapidly and is often advanced when diagnosed. Its morphology is similar to that of advanced adenocarcinoma, which differs from that of neuroendocrine tumors (G1 or G2) generally presenting as a submucosal tumor with or without dille.

MANEC also acts as an aggressive tumor and presents at an advanced stage. Most studies indicate that MANEC

Fig. 2. **a** Boundary area between the two components of rectal mixed adenoneuroendocrine carcinoma on HE staining. **b** Neuroendocrine components with strong synaptophysin immunoreactivity.

generally forms a semicircular tumor with deep ulceration (type 2 tumor) [3–6] or presents as a prominent tumor (type 1 tumor) occupying the lumen [7]. Furthermore, large tumors occasionally cause colonic intussusception. The shape of MANEC tumors is similar to that of colorectal adenocarcinoma, and, therefore, the morphologic distinction between MANEC and colorectal adenocarcinoma using endoscopic images is difficult (Fig. 1).

Pathological Diagnosis and Histological Classification

Specimen biopsies and pathological examination are crucial for a diagnosis. MANEC is defined by the WHO 2010 classification as a tumor composed of both neuroendocrine carcinoma and adenocarcinoma (Fig. 2). Therefore, tumors previously classified as goblet cell carcinoid (GCC), adenocarcinoma ex GCC, and mixed endocrine-exocrine tumor [8] were excluded from the classification of MANEC because they do not contain a neuroendocrine carcinomatous component. However, GCCs are another important entity, and we should determine the details of this differential diagnosis in clinical practice. GCC tumors are divided into three groups according to their components. Typical GCC (group A) consists of well-defined goblet cells arranged in clusters or in a cohesive linear pattern, with minimal cytologic atypia. Adenocarcinoma ex GCC, signet ring cell type (group B), was defined as goblet cells or signet ring cells in irregular large clusters with a single-cell infiltration pattern and significant cytologic atypia. Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma (group C), was defined by focal evidence of goblet cells, not otherwise morphologi-

cally distinguishable from a poorly differentiated adenocarcinoma. A favorable 5-year survival rate of 100% was revealed in GCC group A patients; in contrast, survival rates of 36 and 0% were shown for group B and group C patients, respectively [9]. Although GCC does not meet the criteria for MANEC, an undifferentiated subtype shows poor outcomes similar to those of MANEC.

The neuroendocrine components of MANEC are classified into small cell or large cell carcinoma. They are morphologically similar to neuroendocrine carcinoma of the lung, and a classification was proposed by La Rosa et al. [10] and Travis et al. [11]. Histologically, small cell carcinoma-type MANEC presents small- or intermediate-sized cells with scant cytoplasm and fusiform nuclei with granular chromatin and inconspicuous nucleoli. In large cell MANEC, the neuroendocrine components present large cells with a polygonal shape, abundant cytoplasm, coarse chromatin, and frequent nucleoli [10, 12]. The incidence and impact on survival of MANEC with regard to this differentiation between components have not been reported. However, a national cohort study concerning gastroenteropancreatic neuroendocrine tumor will be a good reference. Although the survey was not limited to cases of colon and rectum cancer, the incidence rates of large and small cell carcinoma of gastroenteropancreatic neuroendocrine tumor were 61 and 39%, respectively. Additionally, the results revealed that the type of carcinoma did not affect survival (large vs. small cell neuroendocrine carcinoma: HR = 1.10, $p = 0.61$). Currently, there is no different therapeutic strategy proposed for neuroendocrine carcinoma with regard to its histological subtype. Overall, the subtype of MANEC is not

considered to influence patient survival and the treatment modality.

From another pathological viewpoint, MANEC composition is classified as collision, composite, or amphicrine according to the arrangement of the neuroendocrine and glandular cells. In collision tumors, adenocarcinoma and neuroendocrine cells are arranged alongside, suggesting that the tumor originates from two cells. By contrast, these components intermingle in composite tumors, and in amphicrine tumors, neuroendocrine and adenocarcinomatous characteristics appear together within the same tumor cells. Composite and amphicrine tumors are considered to arise from single cells, and multidirectional differentiation results in these histological characteristics [13, 14]. Owing to the histology of collision tumors, biopsy specimens occasionally contain only one of the two carcinoma components, which results in an incorrect pathological diagnosis. Therefore, sufficient tissue samples from various parts of the tumor should be obtained to avoid misdiagnosis.

Staging

Staging is crucial in planning the therapeutic strategy for MANEC. In colorectal adenocarcinomas, regional lymph node involvement is routinely investigated with contrast-enhanced computed tomography (CT). Previous reports have indicated that lymph nodes >1 cm in diameter, 3 or more clustered lymph nodes regardless of size, and an irregular lymph node surface are predictive factors for lymph node involvement with a sensitivity of 66–96.3% [15–25]. In contrast, Kim et al. [26] reported that 24.5% of lymph nodes <5 mm in diameter test positive for metastasis from neuroendocrine tumors, the rate of which increases with the increase in lymph node diameter (6.14- and 2.91-mm diameters of positive and negative lymph nodes, respectively). We also reported in a preliminary study that a lymph node >5 mm in diameter in the pericolic/perirectal field is predictive of lymph node metastasis from neuroendocrine tumors. Smaller lymph nodes are involved in metastasis from neuroendocrine tumors rather than from adenocarcinoma. We suggest that more stringent criteria for lymph node metastasis be applied to MANEC evaluated using CT images; however, evidence on the efficacy of CT for MANEC staging is still lacking.

¹⁸F-fluorodeoxyglucose positron emission tomography is another modality for detecting nodal involvement in neuroendocrine tumors. However, its sensitivity in colorectal adenocarcinoma and neuroendocrine tumors is low (42.9 and 33%, respectively) [27, 28], and, there-

fore, it is inapplicable to MANEC in clinical practice. Rectal magnetic resonance imaging and ultrasonography are the preferred modalities for determining regional lymph node metastasis.

In neuroendocrine carcinoma, a tumor size >2 cm in diameter and invasion into the muscularis propria (T3 and T4) reportedly increased the risk of lymph node metastasis to 80% [29]; however, the clinicopathological risk factors for lymph node metastasis in MANEC have not yet been investigated.

Therapeutic Strategy

Surgical Resection

The North American Neuroendocrine Tumor Society and NCCN guidelines recommend that neuroendocrine tumors >2 cm in diameter that have invaded the muscularis propria as well as tumors with lymphovascular invasion or locoregional lymph node involvement be managed with surgical resection, including low anterior or abdominoperineal resection [30, 31]. In contrast, in colorectal adenocarcinoma, tumors invading the sm3 layer should be managed with resection and lymphadenectomy. Given these criteria for neuroendocrine carcinoma and adenocarcinoma, similar criteria should be applied to colorectal MANEC despite the lack of published studies [29, 32].

The NCCN guidelines recommend the resection of distant metastases from neuroendocrine tumors if complete resection is expected. Several studies on metastatic neuroendocrine tumors have stated that hepatectomy improves the survival rate, with low operative mortality [33–36]. A high rate of symptom control (104 of 108 patients; 96.2%) was also observed, even though the recurrence rate was reported to be 59% [37]. Although studies on neuroendocrine carcinoma or MANEC have not yet been published, surgical resection should be considered for metastases, because it is the only curative treatment option.

Compared with the survival rate of adenocarcinoma patients, that of patients with MANEC is substantially worse, presumably because of the high-grade components of neuroendocrine tumors. Wang et al. [38] reported a poor 2-year survival of 50% of patients after surgical resection. In contrast, survival is favorable if the tumor is removed at an early stage. Watanabe et al. [39] reported a 5-year survival rate of 100% for patients with stage I tumors compared with 72.7 and 65.5% for patients with stage II and stage III tumors, respectively.

Conversion Therapy for Distant Metastases

In patients with MANEC, distant metastases should be resected if possible. If initial resection is impossible because of the tumor size or distribution, conversion therapy after chemotherapy should be considered.

According to the results of the CELIM study, 34% of their patients with initially unresectable liver metastasis from colorectal adenocarcinoma underwent R0 resection after treatment with FOLFOX/FOLFIRI plus cetuximab [35]. In this study, the improved mean overall survival and progression-free survival after resection was 53.9 and 15.4 months, respectively, compared with 21.9 and 6.9 months, respectively, for patients who did not undergo resection [40]. The effectiveness of conversion therapy with a 5-fluorouracil (5-FU)-based regimen is apparent in metastatic colorectal adenocarcinoma.

In contrast, the regimen for neuroendocrine carcinoma differs from that for adenocarcinoma and is based primarily on *cis*-diamminedichloroplatinum administration. The mixed histology of MANEC complicates its management. Watanabe et al. [39] reported that the immunohistochemical staining of metastasized tissue in 9 patients with recurrent MANEC demonstrated a neuroendocrine carcinomatous component in 5 patients and an adenocarcinomatous component in 4 patients. These results indicate that in most patients with MANEC, only one of the two components metastasizes and that the histology of distant metastases should be confirmed by biopsy before planning a chemotherapeutic strategy for managing initially unresectable metastases.

Neoadjuvant Chemoradiotherapy for Rectal MANEC

The results of the Swedish Rectal Trial demonstrate that compared with surgery alone, the addition of preoperative radiotherapy improves survival in advanced rectal adenocarcinoma [41]. Furthermore, the FFCO 9203 trial demonstrated that preoperative radiotherapy with 5-FU and leucovorin (LV) is superior to preoperative radiotherapy, with improved late local control [42]. In addition, a high rate of sphincter preservation is a benefit from preoperative chemoradiotherapy [43]. Therefore, preoperative chemoradiotherapy was standardized for tumors classified as T3–4/N any lower rectal adenocarcinoma in Europe and the USA [44, 45]. On the contrary, few physicians have performed preoperative chemoradiotherapy for neuroendocrine tumors, and its efficacy remains uncertain [46, 47]. Because the nature of neuroendocrine carcinoma is similar to that of small cell carcinoma, a substantial response to chemoradiotherapy is expected [48]. Therefore, neoadjuvant treatment for

MANEC is justified, and future studies should investigate this modality.

We reported the case of a 54-year-old woman who underwent preoperative chemoradiotherapy for lower rectal MANEC. Although this treatment is not standardized for MANEC in Japan, we performed chemoradiotherapy (50.4 Gy/28 Fr; tegafur-uracil, 500 mg/day) because only the adenocarcinomatous component (tub2+por) was observed in the colonoscopically biopsied specimen before treatment. After chemoradiotherapy, the tumor shrunk, and the ulcer bed was substantially reduced (Fig. 1). Six weeks later, the patient underwent lower abdominal rectal resection and removal of the right lateral lymph nodes for evaluation of suspected metastasis. The specimen demonstrated MANEC (small cell carcinoma > tub1+tub2) without regional lymph node metastasis. Although the rates of response to preoperative chemoradiotherapy appear promising, the components of the target cells should be examined further when planning chemoradiotherapy (cisplatin or 5-FU based), and the impact on survival should be discussed.

Adjuvant Treatment

Because of the high recurrence rate and poor outcome, adjuvant treatment is recommended for neuroendocrine carcinoma after R0 resection. A regimen based on cisplatin with etoposide or topotecan, a FOLFOX regimen, a vincristine-based regimen with Adriamycin, or a regimen based on carboplatin and etoposide are reported candidates for treating neuroendocrine carcinoma [30, 31, 47], and adjuvant radiotherapy is also recommended for improved survival. The introduction of platinum-oriented adjuvant treatment or radiation for neuroendocrine carcinoma was based on the use of these regimens for small cell lung carcinoma, which shows a histological similarity to small cell neuroendocrine carcinoma. In addition, an efficacy of adjuvant chemoradiotherapy for large cell neuroendocrine carcinoma was also reported [49]; therefore, these regimens should also be candidates regardless of the MANEC subtype [39, 50], though substantial evidence on their efficacy is lacking because most of them have been reported in case series studies.

Management of Recurrent or Unresectable Tumors

Because of its aggressive nature, colorectal MANEC is often diagnosed at an advanced stage and may not be amenable for surgical resection. In such cases, chemotherapy plays a primary role in treatment. Because MANEC comprises two components that have different responses to chemotherapy, clinicians must determine which component to target.

Table 2. Proposed regimens for unresectable colorectal MANEC when the target lesion is predominantly neuroendocrine carcinomatous

Study [Ref.]	Patients, <i>n</i>	Involvement	Regimen	Response rate, %	Survival, months
Mitry [58]	41	Gastroenteropancreatic	Etoposide + cisplatin	CR: 9.8 PR: 31.7 SD: 34.1 PD: 24.4	OS: 15 PFS: 8.9
Hainsworth [61]	78	Various sites (gastrointestinal, lung, skin, prostate, and others)	Paclitaxel + carboplatin + etoposide	CR: 15 PR: 37 SD: 30 PD: 9	OS: 14.5 PFS: 7.5
Raymond [67]	86	Pancreas	Sunitinib	CR: 2.3 PR: 7	PFS: 11.4
Yamaguchi [59]	142	Gastrointestinal	Irinotecan + cisplatin	CR + PR: 51	OS: 13.4 PFS: 5.4
Yao [65]	205	Gastrointestinal, lung	Everolimus	PR: 4 SD: 81	PFS: 11.0

Evidence is provided for neuroendocrine carcinoma. MANEC, mixed adenoneuroendocrine carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; PFS, progression-free survival.

A previous report noted that either of the two components can be present in metastatic lesions [39]; therefore, a biopsy of the recurrent lesion or a distant metastasis can confirm which MANEC component is predominant, which aids in regimen selection [39]. Somatostatin receptor scintigraphy is an effective modality for detecting the neuroendocrine carcinoma component in target lesions. Binderup et al. [51] reported that 69% of high-grade neuroendocrine tumors exhibit positive somatostatin receptor (SSTR) scintigraphy findings.

If the target lesion has an adenocarcinoma component, established regimens for colorectal adenocarcinoma are options for treatment. Oxaliplatin should be added to 5-FU/L-LV as a first-line regimen because it improves the response rate compared with that to 5-FU/L-LV alone (50.7 and 22.3%, respectively) and increases progression-free survival (9.0 and 6.2 months, respectively) [52]. Combination therapy with bevacizumab should also be considered, given that Tyagi and Grothey [53] reported a median progression-free survival of 9.4 months and an overall survival of 21.3 months using this agent. For wild-type K-ras tumors, an anti-epidermal growth factor receptor agent contributed to improved survival in the OPUS trial [54]. If the performance status is unaffected

after failure of these regimens, TAS-102 or regorafenib are alternatives for palliative chemotherapy [55–57].

If the target lesion predominantly comprises a neuroendocrine carcinoma component, cisplatin plus etoposide, which offers a response rate of 41.5% and a median progression-free survival of 8.9 months, should be considered as a first-line regimen [58]. Yamaguchi et al. [59, 60] reported that the combination of cisplatin and irinotecan offers a response rate of 51% and a progression-free survival of 5.2 months for neuroendocrine carcinomas of various organs, as well as an overall survival of 7.6 months for colorectal neuroendocrine carcinomas in particular. Hainsworth et al. [61] used a more aggressive regimen including paclitaxel, carboplatin, and etoposide and reported a response rate of 53% (complete response rate: 15%) and a median progression-free survival of 7.5 months. In addition to these cytotoxic regimens, everolimus, an oral inhibitor of mechanistic target of rapamycin (mTOR) is a candidate for treating unresectable neuroendocrine tumors. Although mutations of mTOR pathway genes are infrequently detected in gastrointestinal neuroendocrine tumors, mTOR overexpression and its downstream activity are implicated in adverse clinical outcomes [62, 63].

In RADIANT-4, a phase III trial, everolimus was demonstrated to be superior to placebo for improving the median progression-free survival with gastrointestinal or lung neuroendocrine tumors (11.0 and 3.9 months, respectively) [64, 65]. Sunitinib malate, an oral multi-target tyrosine kinase inhibitor, inhibits the signal transduction of the vascular endothelial growth factor receptor and platelet-derived growth factor receptor pathways, stem-cell factor receptor, and glial cell-derived neurotrophic factor [66]. A phase III trial of patients with low-to-intermediate progressive pancreatic neuroendocrine tumors demonstrated improved progression-free survival with sunitinib malate compared with best supportive care (11.1 and 5.5 months, respectively) [67], although evidence on the effectiveness of this agent for treating gastrointestinal neuroendocrine carcinoma is lacking (Table 2).

The introduction of somatostatin analogs (SSA) for neuroendocrine tumor is a therapeutic option for G1 and G2 neuroendocrine tumor [68]. Octreotide and lanreotide, well-known SSA, have high affinity for SSTR-2 and -5. However, it has been reported that SSTR-5 was expressed in 0% of neuroendocrine carcinomas, while it was positive in 81.8 and 60% of G1 and G2 neuroendocrine tumors, respectively [69, 70]. Conversely, only a single study showed a 100% SSTR-2 expression rate in gas-

troenteropancreatic neuroendocrine carcinoma [69], but this study included only one rectal neuroendocrine carcinoma case, which is inadequate evidence to support the introduction of SSA for neuroendocrine carcinoma components.

A previous study has revealed that the exocrine and endocrine components of MANEC have a common genetic alteration, indicating that both components have a common oncogenic pathway from the same cellular origin. Vortmeyer et al. [71] showed that both components had identical loss of heterozygosity in *APC*, *DCC*, and *TP53* in a series of 7 patients. A recent study [72] showed that *KRAS* mutations on the identical locus in both tumor components were present in 57% (4 out of 7) of their MANEC patients. *KRAS* is known as a molecular predictor of the efficacy of anti-EGFR drugs in colorectal adenocarcinoma. Although sufficient evidence is lacking, these common genetic alterations would be a possible target for molecular therapy.

If patients present with paraneoplastic symptoms, such as bowel obstruction, surgery is an alternative, particularly when the tumor is unresponsive to chemotherapy. Debulking is appropriate only when >90% of the tumor is reduced [30, 31]. If sufficient tumor reduction is not expected, options such as bypass or stoma creation should be considered.

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